REMARKS

Reconsideration and withdrawal of the rejections of the application are requested in view of the amendments and remarks presented herein, which place the application into condition for allowance. The Examiner is thanked for indicating that the Petition to Amend Inventorship has been granted.

I. STATUS OF CLAIMS AND FORMAL MATTERS

Claims 2, 4-9, 12-21, 28, 34, 35 and 38 are under consideration. Claim 2 is amended to incorporate the recitation of cancelled claim 41. The remaining amendments to claims 2, 4-6, 13 and 15 are for clarity and do not affect the scope of the claims. No new matter is added.

It is submitted that the claims, herewith and as originally presented, are patentably distinct over the prior art, and that these claims are and were in full compliance with the requirements of 35 U.S.C. § 112. The amendments of and additions to the claims, as presented herein, are not made for purposes of patentability within the meaning of 35 U.S.C. §§ 101, 102, 103 or 112. Rather, these amendments and additions are made simply for clarification and to round out the scope of protection to which Applicants are entitled. Furthermore, it is explicitly stated that these amendments should not give rise to any estoppel, as they are not narrowing amendments.

II. THE REJECTION UNDER 35 U.S.C. § 112, 2ND PARAGRAPH, IS OVERCOME

Claims 2, 4-9, 12-21, 28, 34, 35, 38 and 41 were rejected under 35 U.S.C. § 112, second paragraph, as allegedly being indefinite. The rejection is traversed.

The Office Action states that the recitation "part thereof" in claim 2 is inconsistent with paragraph (i) of claim 2. The phrase "or part thereof" has been added to paragraph (i) where "the CDR loop structure" is recited, to maintain consistency between the recitations. In addition, for the sake of consistency, "or part thereof" has been added to the dependent claims (4-6, 13, and 15) that refer to "the CDR loop structure."

In view of the foregoing, reconsideration and withdrawal of the indefiniteness rejection is requested.

III. THE REJECTION UNDER 35 U.S.C. § 102 IS OVERCOME

Claims 2, 7-9, 12, 13, 20, 21, 28, 34, 35, 38 and 41 were rejected under 35 U.S.C. § 102(b) as allegedly being anticipated by Peach *et al.* The rejection is traversed.

The Office Action alleges on page 4 that Peach teaches CTLA-4 and CD28 ligands in which the V-like domains have been modified or replaced such that the size of the CDR loop structure has been altered. This is an incorrect interpretation of the teachings of Peach. Rather, Peach discusses (i) point mutations in the CDR3-like loop structure (see page 2051), and (ii) replacement of small "regions" of CD28-Ig with homologous regions from CTLA-4 Ig. The regions replaced are adjacent the MYPPY hexapeptide in the CDR3-like loop as well as in the CDR1- and CDR2-like loops (see page 2052, Figure 3 and Table 2 of Peach). Nowhere does Peach disclose or suggest increasing the size of a CDR loop structure or part thereof by one or more amino acid residues. Therefore, as the current claims read on the size of the CDR loop structure or part thereof being increased by at least one amino acid residue, they are clearly not anticipated by Peach.

Furthermore, in the obviousness rejection over Peach and Koide on page 10 of the Office Action, the Examiner states: *"Peach et al. do not teach modified monomeric non-antibody ligands wherein the size of the CDR loop structure has been increased by at least nine amino acids. . . ."* This implies that the Examiner considers Peach to teach increasing the size by at least one, two or six amino acids, which contradicts the rejection under Section 102(b), which does not include claims 4 and 5, directed to increasing the size by two and six amino acid residues, respectively. It is true that Peach does not teach modified ligands wherein the size of the CDR loop structure has been increased by at least nine amino acids. As discussed above, it is also true that Peach does not teach increasing the size of the CDR loop structure by any number of amino acids.

In view of the foregoing, reconsideration and withdrawal of the anticipation rejection are requested.

V. THE REJECTIONS UNDER 35 U.S.C. §103 ARE OVERCOME

Claims 2, 13 and 14 were rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over Peach *et al.* in view of Bogden *et al.* Claims 2 and 15-17 were rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over Peach *et al.* in view of Cai *et al.* The rejections are traversed, and will be addressed collectively.

In previous Office Actions, these same objections were raised based on the teaching of Koide in combination with Bogden and Cai, respectively. Limiting the main claims to VLDs derived from CTLA-4, CD28 and ICOS overcame these objections. The Examiner now argues

that Peach discloses CTLA-4 and CD28 ligands in which the VLD has been modified or replaced such that the size of the CDR loop structure has been altered. Claim 2 has been amended to recite that the size of the CDR loop structure or part thereof is increased by at least one amino acid residue. As discussed above, nowhere does Peach disclose or suggest replacing a CDR loop structure or part thereof with a longer sequence, as is now required by claims 2, 13 and 15.

Furthermore, there is nothing in either of Bogden or Cai suggesting that polypeptides derived from somatostatin and the human anti-melanoma antibody V86, respectively, should or could be incorporated into a monomeric VLD. Additionally, even if the skilled person were to consider incorporating the polypeptides from Bogden or Cai into some sort of display vehicle, the selection of the monomeric VLDs derived from the specific subset of ligands being claimed cannot not be considered obvious. Even if the skilled person were aware of Peach, Peach is not concerned with incorporating and displaying "foreign" sequences. Peach is concerned with investigating the binding of CTLA-4-Ig and CD28-Ig to B7-1, and concludes from its investigations that the *"results presented . . . suggest that this approach should be evaluated as a means of obtaining peptide inhibitors of molecular interaction between CTLA-4/CD28 family members and B7-related molecules"* (last sentence of Peach).

In conclusion, there is no incentive for the skilled person to combine the teachings of Peach with either of Bogden or Cai. Even if the skilled person were to hypothetically combine the teachings of Peach with either of Bogden or Cai, they would not arrive at the invention. If anything, they would be led away from the invention as all Peach teaches is that point mutant and homologue mutant proteins of CTLA-4 and CD28 can be prepared. Finally, there would not be a reasonable expectation of success if such a combination were to be followed - it would be entirely speculative.

Claims 2, 4-6, 18 and 19 were rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over Peach *et al.* in view of Koide. The rejection is traversed.

Koide concerns loop regions corresponding to wild-type fibronectin type III (Fn3) loop regions that may be varied by the insertion of from 2 to 25 amino acids. The Office Action has taken this teaching and combined it with that of Peach, concluding that it would be obvious for the skilled person to insert one or more amino acids into the CDR loop structures of CLTA-4, CD28 or ICOS as claimed in claim 2 of the present invention.

We have previously argued that Koide relates to Fn3 domains, which are very different from the V-like domains (VLDs) of the present invention. The Examiner does not appear to accept this fact, stating on page 10 of the Office Action that claim 5 of Koide teaches a modified monomeric V-like ligand that varies from unmodified ligands by an insertion of from 2 to 25 amino acids. To the contrary, Koide is concerned throughout with Fn3 polypeptides and not with VLDs. Fn3 domains are very different to the VLDs encompassed by the present invention. In particular, Figures 1A and 1B in Koide clearly show that the number of beta strands in the Fn3 structure differs significantly from that in VLDs. This key feature makes the Fn3 domain different from the antibody V-like domain.

With respect to the assertion that Koide teaches insertion of up to 25 amino acids, it should be noted the disclosure of Koide must be read and considered in its entirety. As such, the skilled person on reading Koide in its entirety would understand the following. First, although Koide claims loops with insertions of from 2 to 25 amino acids, in the construction of the modified Fn3 scaffolds as described in the Examples, loops of only 5 residues led to high flexibility, causing very low affinity binding to targets. As a result, libraries were constructed which had very small loops, *i.e.* less than 5 amino acids, in order to produce binding molecules (see paragraph 166). This is in stark contrast to the present invention, where a somatostatin loop of 14 residues was required for binding and functional activity. Based on the teaching of Koide, it would appear unlikely that a loop of this length would be functional if inserted into Fn3. Certainly, the skilled person upon reading Koide in its entirety would conclude that the scaffolds were of limited use as regards the size of inserts that could be employed.

Second, although Koide performs several binding assays against various antigens, only one Fn3-based construct is fully analyzed. This single construct, called Ubi4-Fn3, is an isolate that dominates in binding Ubiquitin.

Finally, although Koide mentions that loops of the Fn3 domain can be replaced with loop structures derived from antibodies, no functional binding data is provided. There is no evidence to suggest that the constructed molecule has any function or is able to bind to the target molecule. From the data presented in the application, it is purely speculative as to whether any other fragment would have activity if inserted into Fn3. Therefore, the teachings of Koide are not enabling for the present invention.

The Office Action contends that Koide teaches that the ability to label the Fn3 ligands with radioisotopes make them an ideal model system for NMR studies on protein-protein interactions. In fact, Koide describes, in paragraph 135, the labelling of both Fn3 and a domain of staphylococcal protein G, in the hope of creating a labelled complex and thus possibly making *"the complexes an ideal model for NMR studies on protein-protein interactions."* In other words, Koide does not teach that labelled Fn3 domains as such are ideal candidates for studying protein-protein interactions but rather that the complexes with protein G are ideal candidates. Koide certainly does not teach the labelling of VLD molecules, as these are distinctly different molecules, as discussed above.

The first paragraph on page 11 of the Office Action states that it would have been obvious to the skilled person to apply the teachings of Koide to those of Peach to arrive at the claimed modified monomeric non-antibody ligands linked to a radioisotope, or those with increased CDR loop structures. First, as outlined above, Applicants do not agree with the Examiner's assessment of what Koide teaches. Second, there is no incentive for the skilled person to take the teaching of Koide and combine it with what is taught by Peach. Evidence to the contrary is lacking.

The Office Action further states that the skilled person so motivated, would have a reasonable expectation of success because the teachings of Koide state that it is possible and highly desirable to label modified monomeric non-antibody ligands with a radioisotope for NMR studies. As discussed above, Koide does not teach that it is possible and highly desirable to label modified monomeric non-antibody ligands with a radioisotope for NMR studies. In contrast, Koide teaches in paragraph 135 that: *"The resulting Fn3-protein G complexes (about 150 residues) is [sic] one of the smallest protein-protein complexes produced to date, well within the range of direct NMR methods. The small size, the high stability and the solubility of both components and the ability to label each with stable isotopes . . . make the complexes an ideal model system for NMR studies on protein-protein interactions."* Indeed, if the skilled person were to take the teaching of Koide from paragraph 135, then they would form a complex of a VLD with protein G in order to study protein-protein interactions, and would not arrive at the instant invention. Therefore, there is no reasonable expectation of success.

As discussed above, there is nothing in Peach indicating that CTLA-4 or CD28 VLDs can be used as scaffold structures. Furthermore, there is nothing in Peach indicating that the size

of the CDR loop structures may be modified by increasing the number of amino acids as is now required by amended claim 2. Furthermore, there is nothing in Peach indicating to the skilled person that, should they even consider increasing the size of a CDR loop structure or part thereof, there is a reasonable chance of success. Any such investigation would be purely speculative.

In fact, Peach teaches away from the present invention. Peach teaches the preparation and testing of hybrid molecules in which the V-like extracellular domain of CD28 has been mutated in the CDR loops through replacement with the homologous regions from CTLA-4. This was to enable Peach to study which regions in CTLA-4/CD28 are important for binding to their native receptor B7-1. Peach states: *"Hybrid molecules which include the CTLA-4 CDR3- and CDR1- like regions did not fully restore wild-type CTLA-4-Ig binding activity. This suggests that other residues in CLTA-4 also contribute to binding"* (page 2056, right hand column, second paragraph). In other words, Peach suggests that replacing CDRs alone is insufficient to confer relevant target binding in CTLA-4.

The finding that the VLDs of the present invention, *e.g.* CTLA-4 and CD28, could provide a scaffold capable of functionally displaying insertions which, for example, increased the size of the CDR loop structure by 15 amino acid residues (see construct 2V8, discussed in Example 4 and Figures 6 and 10) is highly surprising and represents a significant advancement over what is taught in Koide.

Accordingly, reconsideration and withdrawal of the rejections under 35 U.S.C. § 103 are requested.

CONCLUSION

Applicants note that the present Examiner is the fifth Examiner to be assigned to this application. The piecemeal examination that has predominated in this case has led to inefficiencies and unnecessary expenditures by both Applicants and the PTO, as well as extreme prejudice to Applicants in terms of shortened patent protection. Accordingly, if there are any further impediments to allowance of the pending claims that might be resolved telephonically, the Examiner is requested to contact the undersigned, in an attempt to avoid further delays in prosecution.

Respectfully submitted,

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